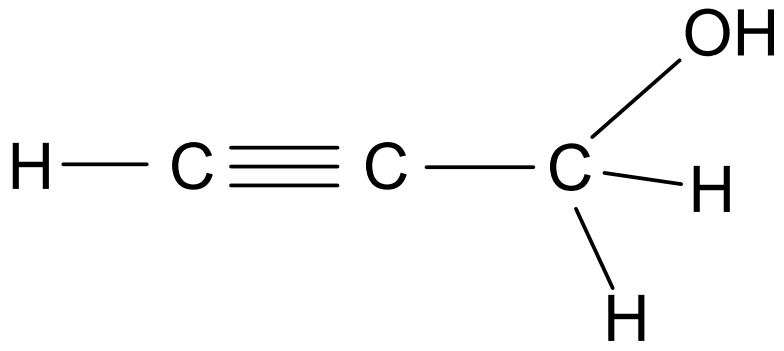
201-14641A

Propargyl Alcohol



CAS Number 107-19-7

U.S. EPA HPV Challenge Program
Revised Submission

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Executive Overview

Propargyl alcohol CAS no. 616-45-4 is a three-carbon acetylenic alcohol, which can be prepared by several routes. It is a clear liquid with a geranium-like odor and with moderate volatility. It is miscible with water and polar organic solvents. The freezing point is in the range of -50° C, the boiling point at 1013 hPa is 114-115° C, the vapor pressure at 20°C is 15.5 hPa and its log $K_{o/w}$ is –0.35. Its uses span a wide range of applications including, reactant/chemical intermediate, corrosion inhibitor, solvent stabilizer, soil fumigant and polymer modifier.

In the environment, based on physicochemical data and experimental data, Propargyl alcohol will not bioaccumulate and will distribute primarily to water where it will be subject to volatilization and rapid biodegradation. It is expected to react rapidly with atmospheric hydroxyl radicals with a half-life of 12 hours. As there are no consumer applications for Propargyl alcohol, and as the material is readily biodegradable, there should be no significant releases to water. The toxicity of Propargyl alcohol to aquatic species is moderate to high, with an LC_{50} for freshwater fish in the range of 1-5 mg/L. Data for daphnids define the toxic potential of Propargyl alcohol for invertebrates but data for algae toxicity are limited.

Pharmacokinetic data show that Propargyl alcohol is rapidly absorbed and distributed after oral or inhalation exposure. Excretion is also rapid with extensive metabolism to carbon dioxide. The enzyme CYP 2E1 has been identified as primarily responsible for activation of Propargyl alcohol to its biologically reactive aldehyde.

Multiple determinations of the oral LD_{50} of Propargyl alcohol have been reported in a range of 50 to 100 mg/kg-bw. The approximate 1-hr LC_{50} for Propargyl alcohol has been established with relatively high confidence by a combination of two studies and is in the range of 1000-1200 ppm. The dermal LD_{50} has been reported as 88 mg/kg-bw in rabbits but dermal absorption can be low due to the volatility of this material.

There are several studies of Propargyl alcohol extending for 14 or 90-day periods by the three major routes of exposure. The systemic NOAEL is low with liver and kidney being target organs.

Genotoxicity studies have shown little potential for genotoxicity activity in vitro or in vivo. An inhalation carcinogenicity study in rats and mice is ongoing with the National Toxicology Program (start date 09/2001).

Although subchronic studies have not shown any specific damage to reproductive organs, there is no specific data available on the developmental or reproductive toxicity of Propargyl alcohol.

The overall conclusion is the information is adequate for all the HPV data elements except reproduction and development and the daphnia and algae data are weak. An OECD 421 test is recommended to establish reliable information for reproductive and developmental endpoints and OECD 201 and 202 tests are recommended to strengthen the information for aquatic toxicity.

Testing Plan and Rationale

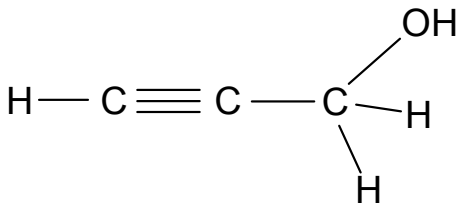
Testing Plan in Tabular Format

CAS Number 107-19-7 Propargyl Alcohol	Information Available?	OECD Study ?	GLP Study?	Supporting Information?	Estimation Method?	Acceptable?	Testing Recommended?	
HPV Endpoint								
Physical Chemical								
Melting Point	Y	N	N	N	N	Y	N	
Boiling Point	Y	N	N	N	N	Y	N	
Vapor Pressure	Y	N	N	Y	N	Y	N	
Partition Coefficient	Y	Y	N	Y	N	Y	N	
Water Solubility	Y	N	N	Y	N	Y	N	
Environmental & Fate								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	N	N	Y	N	Y	N	
Ecotoxicity								
96-Hour Fish	Y	N	N	Y	N	Y	N	
48-Hour Invertebrate	Y	N	N	Y	N	Y	Y	
4-Day Algae	N	N	N	Y	N	N	Y	
Toxicity								
Acute	Y	N	N	Y	N	Y	N	
Repeated Dose	Y	N	Y	Y	N	Y	N	
Genetic Toxicology *in vitro*	Y	N	N	Y	N	Y	N	
Genetic Toxicology *in vivo*	Y	Y	Y	Y	N	Y	N	
Reproductive	Y	N	Y	Y	N	N	Y	
Developmental	N	N	N	Y	N	N	Y	

Introduction

Propargyl alcohol, CAS no. 107-19-7, is a three-carbon acetylenic alcohol, which can be prepared by several routes. These include preparation from acetylene using a high-pressure synthesis (1) and as a by-product of the commercial synthesis of butynediol (2).

It is a clear liquid with a geranium-like odor. It has moderate volatility and is miscible with water and polar organic solvents. Its uses span a wide range of applications including, reactant/chemical intermediate, corrosion inhibitor, solvent stabilizer, soil fumigant and polymer modifier (12). Its structure is shown below:



Propargyl alcohol is also known as:

- Propynyl alcohol
- 2-Propynol
- 2-Propynyl alcohol
- 1-Hydroxy-2-propyne
- 1-Propyn-3-ol
- 1-Propyn-3-yl alcohol
- 3-Hydroxy-1-propyne
- 3-Propynol
- Ethynylcarbinol

Exposure in industrial applications is limited by process controls and protective equipment. Inhalation and dermal exposure are considered the primary routes of occupational exposure. The ACGIH TLV is 1 ppm with a skin notation. The basis for this TLV is stated as the similarity of Propargyl alcohol to Allyl alcohol in structure and in toxicity (3). There are no known consumer uses for Propargyl alcohol; thus, no consumer exposure in known to occur.

Several physicochemical, fate and toxicity studies have been conducted on Propargyl alcohol. These studies are briefly reviewed in this testing rationale document, which also describes how these studies meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. The available data set satisfactorily fulfills most of the data requirements for the EPA HPV Program.

The majority of data elements are filled by high-reliability studies on Propargyl alcohol, where direct data are not available or data are sparse, surrogates and estimation are used to fill the data element where appropriate. This is encouraged by the U.S. EPA and other regulatory authorities to avoid unnecessary testing cost and animal usage. After review of the existing data and examination of surrogates and modeling, the data elements for reproductive and developmental toxicity remain unfilled.

Metabolism, Mechanism of Action and Pharmacokinetics

Absorption-Distribution-Metabolism-Excretion (ADME) data developed by the National Toxicology Program (4) show that Propargyl alcohol is quickly distributed and excreted following an intravenous dose. The majority of the radioactivity (^{14}C-labeled test material) was excreted in the urine and as carbon dioxide in the breath of both rats and mice. Oral dosing resulted in a similar rapid (but slower than after i.v. dosing) excretion pattern, with the bulk of radioactivity being excreted in the urine and exhaled carbon dioxide. Dermal absorption was low due to the volatility of Propargyl alcohol. Inhalation exposure resulted in 55 to 63% absorption of inhaled Propargyl alcohol at 1 or 10 ppm and only 23-33% absorption at 100 ppm. Both species eliminated the majority of the inhaled dose in urine. Chromatographic analysis indicated that Propargyl alcohol is extensively metabolized and one metabolite was identified as a glutathione conjugate. It was assumed that there are multiple glutathione conjugates across the triple bond as was demonstrated by Banijamali et al. in a recent publication (5)

Mechanism of Activation and Metabolism

Studies in the mid 1990's by DeMaster and coworkers (6) reported that, while oxidative metabolism of low molecular weight primary alcohols is generally accepted to be catalyzed by alcohol dehydrogenase, Propargyl alcohol is a relatively poor substrate for this enzyme. They studied the metabolism of Propargyl alcohol by the catalase alternative pathway. Bovine liver catalase was used, to measure the rate of oxidative bioactivation of Propargyl alcohol to 2-Propyn-l-al. They found the rate to be higher than predicted by modeling and hypothesized that the oxidative biotransformation of Propargyl alcohol to the more reactive α,β-unsaturated aldehyde by liver catalase might be the initial step in Propargyl alcohol induced liver injury.

Moridani and coworkers (7) recently showed that inactivation of catalase in isolated hepatocytes only partially inhibited the toxicity of Propargyl alcohol. They went on to demonstrate that Propargyl alcohol-induced cytotoxicity, rapid GSH depletion and reactive oxygen species (ROS) formation involves metabolic activation by cytochrome P450 rather than catalase or alcohol dehydrogenase. Using specific induction and depletion they demonstrated that CYP 2E1 was the enzyme responsible for activation of Propargyl alcohol to its aldehyde, 2-Propyn-1-al. This is in contrast to the activation of Allyl alcohol, which is oxidized to its cytotoxic aldehyde, Acrolein, by alcohol dehydrogenase. They postulated the metabolic scheme below based on their data:

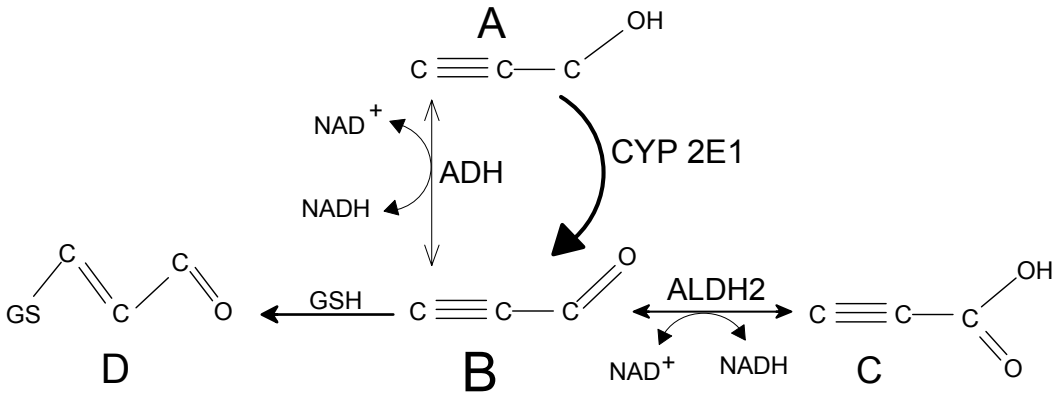


Figure 1. Proposed Bioactivation and Metabolism of Propargyl Alcohol

In this scheme, Propargyl alcohol (A) is oxidized primarily by CYP 2E1, with a minor contribution by alcohol dehydrogenase, to 2-Propyn-1-al (B). The aldehyde is a chemically active species that can attack vital cellular macromolecules but reacts preferentially with glutathione to form conjugates that undergo urinary excretion. An alternative pathway for the aldehyde is further enzymatic oxidation via aldehyde dehydrogenase to Propiolic acid (C), which could be further, oxidized, conjugated and excreted, or be converted back into the aldehyde. Its ability to react with glutathione and cellular macromolecules is not known.

Mechanistically, they demonstrated depletion of glutathione and formation of ROS (Reactive Oxygen Species), which lends support to the proposed mechanism. This mechanism is also consistent with the recent NTP ADME results present briefly above, is coherent with basic chemical and biochemical principles and is consistent with the organ effects (liver as primary systemic target) seen in the subchronic studies. A relatively-high degree of dermal toxicity is also predicted by this model as oral administration would be expected to result in significant "first-pass metabolism" whereas dermal administration should lead to relatively higher concentrations in the CNS that could effect mortality in experimental animals.

This mechanism is considered highly plausible and is supported by the known data. Some details, such as the role of the Propolic acid (which could be biochemically active, as it has potential for 1,4-addition type reaction) and distribution of the aldehyde remain to be elucidated.

Physicochemical Data

Physicochemical data for Propargyl alcohol are available from the literature and are confirmed by manufacturer's information.

Melting Point	-52 to –48° C (8)
Boiling Point	114 - 115° C @ 1013 hPa (8)
Vapor Pressure	15.5 hPa @ 20˚ C (9)
Partition Coefficient	Log $K_{o/w}$ = -0.35 (10)
Water Solubility	Soluble in all proportions (8)

Table 1: Physicochemical Properties of Propargyl Alcohol

These properties indicate that Propargyl alcohol is a moderately volatile liquid with high water solubility. The value of the partition coefficient suggests that Propargyl alcohol will partition preferentially into water and, therefore, has little potential for bioaccumulation.

Recommendation: No additional physicochemical studies are recommended. The available data fill the HPV required data elements.

Environmental Fate and Pathways

Biodegradation potential for Propargyl alcohol has been determined by the Chemicals Evaluation and Research Institute, Japan using the MITI protocol. In this study, the BOD reached 95% of theoretical after 28 days incubation of a 100mg/L concentration of test substance using activated sludge at 30 mg/L (11). In addition to this result, there is also a BOD_{20} test that has been conducted that provided a 20-day BOD:COD ratio of 0.61 (12). The kinetics were measured at 5 and 10 days where the BOD/COD ratio was 0 and 0.39, respectively. The source or adaptation state of the inoculum was not disclosed in this BOD_{20} test.

This result is supported by the BIOWIN (v4.00) estimate that predicts rapid biodegradation from all of its models (see robust summary). In their comments to the consortium on the initial test plan and robust summaries, EPA identified studies in addition to the one cited above. Initial attempts to find all the EPA referenced studies were

not successful, and since the studies found are satisfactory for the HPV program, more extensive efforts to get these additional references were not made. The additional studies were 1986 report from Petrolite (13), which was previously obtained and found to be not relevant to pure Propargyl alcohol; a 1975 publication by Dore, et al. (14) from the French literature; and a 1989 EPA report by Loehr (15) relating to the treatability of soils. Overall the data are sufficient to demonstrate that this material is readily biodegradable.

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The program produced a estimated rate constant of 10.4 E-12 cm^3/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of Propargyl alcohol with hydroxyl radical, the estimated half-life of Propargyl alcohol vapor in air is approximately 12.3 hours (see accompanying robust summary). Based on the structure, it is also estimated that Propargyl alcohol vapor will react with atmospheric ozone but this reaction will be insignificant compared with the hydroxyl radical reaction rate.

Water stability has not been quantitatively determined for Propargyl alcohol. Quantitative stability determinations (e.g. OECD 111) are considered unnecessary for compounds containing only non-hydrolysable groups, as the SIDS manual states that consideration should be given to using an estimation method. There is no evidence available that Propargyl alcohol is unstable in water, and it has no hydrolysable groups. Both the alkyene and alcohol moieties are considered generally resistant to hydrolysis by Harris (16). A more thorough rationale is presented in the attached robust summary.

Theoretical Distribution (Fugacity) of Propargyl alcohol in the environment was estimated using the MacKay EQC level III model with standard defaults in EPIWIN v 3.05 but using the measured vapor pressure and the measured log $K_{o/w}$ (17). The results for distribution using a model calculated $K_{o/c}$ (adsorption coefficient based on organic carbon content) of 0.183 and equal initial distribution to air, water and soil are:

- Air 3.1 %
- Water 53.6 %
- Soil 43.2 %
- Sediment 0.09 %

Recommendation: No additional fate studies are recommended. The available data fill the HPV required endpoints.

Ecotoxicity

Flow though studies of acute fish toxicity using measured concentrations of Propargyl alcohol are available demonstrating a moderate to high hazard (LC_{50} = 1.5 mg/L) to fathead minnows after 96 hours of exposure. A static test using the golden orfe provided a higher (4.6 mg/L) LC_{50}. Daphnia studies indicate an EC_{50} in the area of 25 mg/L. The two values reported in the table below for Daphnia were obtained by the same investigators using the same method, except that reconstituted freshwater was used to generate the higher value and tap water to generate the lower value. Algae growth inhibition was determined using a standardized procedure as a threshold of toxicity value (EC_{03}) to be 18 mg/L in an 8-day test. These values with references are shown in the table along with results of ECOSAR modeling using a specific model for the Propargyl alcohols that was developed by the U.S.EPA. Two sets of estimates are given; the first uses physiochemical parameters as calculated by the SRC software and the second as calculated by the CLOPG software (18). In this case, a measured $K_{o/w}$ value was used to run the ECOSAR prediction and there is no clear way to determine which SAR equation is more appropriate. Use of the neutral organics model gives much higher values due to there being a specific mechanism other than narcosis for aquatic toxicity (19)

Table 2: Aquatic Toxicity of Propargyl alcohol

	Reported Values	ECOSAR Predictions
Fish, 96-hour LC_{50}	1.5 mg/L (20) 4.6 mg/L (21)	4.7 mg/L* 8.5 mg/L**
Daphnia, 24-hour EC_{50}	32 mg/L (22) 11 mg/L (23)	11.4 mg/L* 17.7 mg/L**
Algae, 8-day EC_{03} Algae, 96-hour EC_{50}	18 mg/L (24)	17.7 mg/L* 117 mg/L**

* Estimated using ECOSAR using Propargyl alcohols model based on CLOPG estimates (25)

**Estimated using ECOSAR using Propargyl alcohols model based on SRC estimates (25)

Support that simple alpha-beta unsaturated alcohols have a relatively high degree of aquatic toxicity also comes from data on the analog Allyl alcohol which has been reported to have a 96-hour LC_{50} for fathead minnows of 0.32 mg/L and a 96-hour EC_{50} for *Daphnia magna* in the range of 0.25 to 0.4 mg/L (26).

In spite of this consistency for alpha-beta unsaturated alcohols, the ECOSAR models for "propargly alcohols" are not considered robust as it was developed from only two compounds selected from the series of: alpha-alkynyl alcohols (C#COH), beta-alkynyl alcohols (C#CCOH), and gamma-alkynyl alcohols (C#CCCOH) for fish, daphnids and algae (27). These materials are chemically more different than is apparent from their structures as, conjugation effects are more evident with the beta-alkynyl alcohol (The true Propargyl alcohol). For this reason neither the SCR derived estimate nor the ClogP derived estimate is considered an adequate estimate of the toxicity of Propargyl alcohol to invertebrates and algae. In addition to this thin database of analogs, the consistency of the "excess toxicity"[i] of Propargyl alcohol is impossible to predict across tropic levels on a theoretical basis. The

i Excess toxicity is the difference in the actual toxicity compared with that predicted by the neutral organics model.

excess toxicity for fish is approximately 2000 fold. (2000 is the result of the neutral organic model predicted value from the equation $\log LC_{50} = 1.75 - 0.94 \log K_{ow}$ mmol/L, or 6717 mg/L, divided by the approximate experimental value for the 96-hour fish LC_{50} of 3 mg/L).

It is clear from the limited studies of Propargyl alcohol toxicity on daphnids that the toxicity of this material is much greater than that predicted by the neutral organics models of 6119 mg/L for daphnids[ii]. Based on the fact that the existing daphnid studies gave relatively reproducible results in two studies, that LC_0, LC_{50} and LC_{100} values were obtained, that propargly alcohol evaporation from solution over 24 hours is probably acceptably low, and that highly water-soluble materials with low $\log K_{ow}$ generally have 24 and 48-hour LC_{50} values that do not vary greatly, the daphnia existing studies are considered valuable for hazard and risk assessment under the HPV program. Nevertheless, the consortium realizes that conducting a new definitive guideline study would add an important data point for improvement of the ECOSAR model; therefore, the consortium is planning to conduct an OECD 202 guideline compliant study using *Daphnia magna.*

The limited algae data suggest that the toxicity of this material is much greater than that predicted by the neutral organics models of 3341 mg/L for algae[ii]. The moderate volatility of Propargyl alcohol is likely to be a negative factor in this study of 8-days duration as is the potential for reactivity of Propargyl alcohol with the algal cells. In addition, as the only data point reported is the EC_{03} (toxic threshold) with no slope information available, this study is inadequate to accurately determine the extent of the excess toxicity of Propargyl alcohol to algae. For this reason, the Consortium agrees with EPA's recommendation to conduct an additional study on algae and is proposing to conduct an OECD 201 guideline compliant study define the toxicity of Propargyl alcohol to green algae.

Recommendation: Acute toxicity studies of Propargyl alcohol on daphnids and algae are recommended to increase our knowledge of the toxicity of Propargyl alcohol to these two trophic levels.

ii These values are based on the neutral organics model equations which give the 48-hour daphnid LC50 in mmoles/L as log $LC_{50} = 1.72 - 0.91 \log K_{ow}$, and the 96-hour algal EC_{50} in mmoles/L as $\log EC_{50} = 1.466 - 0.885 \log K_{ow}$.

Health Effects

Acute Toxicity

Oral Exposure

Multiple determinations of the oral LD_{50} of Propargyl alcohol have been reported. Perhaps the most reliable was published in 1985 by Archer (28), who reported an LD_{50} of 110 mg/kg-bw for male Sprague-Dawley rats and an LD_{50} of 55 mg/kg-bw for females of the same strain. These results are confirmed by additional studies, one reporting an LD_{50} of 93 mg/kg for male and 54 mg/kg for female Sprague-Dawley rats (29) and the other reporting an LD_{50} of 56 mg/kg for rats of unspecified sex and strain (30). All of these studies may be found as robust summaries accompanying this test plan.

Inhalation Exposure

The approximate 1-hr LC_{50} for Propargyl alcohol has been established with relatively high confidence by a combination of two studies. The first study, published in 1977 by Vernot (29), contains acute toxicity data for several compounds by different routes of administration. As they conducted analytical measurements on exposure levels and ran enough exposure levels to collect sufficient data for a high-confidence determination, confidence in the results is increased. Their results indicate that female rats are slightly more sensitive than males with a 1-hour LC_{50} of 1040 ppm for females and 1200 ppm for males. The second study was a modern 1-hour limit test conducted at Hazleton Laboratories. In this study using measure concentrations of Propargyl alcohol, it was found that exposure of rats to 1480 ppm for one hour resulted in 100% mortality within a few days of exposure (31). This finding of an LD_{100} at 1480 is in accord with the LC_{50} being in the ranges of 1040-1200 ppm.

Although a standardized 4-hour LC_{50} is not available, this material is anticipated to follow a C times T relationship reasonably well as the mechanism of death is not simply solvent narcosis. In this case, the 4-hour LC_{50} can be estimated to be between 200 and 400 ppm with high confidence.

Dermal Exposure

The dermal LD_{50} of Propargyl alcohol was reported to be 88 mg/kg-bw in rabbits by Vernot in his many-route, multi-compound publication (29). This is a reasonable value in light of the oral and inhalation toxicity data. An interesting note to the potential dermal toxicity is a report that the LD_{lo} for Propargyl alcohol was 15.8 mg/kg- bw when the substance was applied in a solution of Dowanol-50 (32). These glycol ether types of solvents (Dowanol-50 is Dipropyleneglycol monomethyl ether) are thought to enhance the penetration of materials through the skin, or al least interfere with the normal evaporation of the test substance. Based on the strength of these data the skin warning is appropriate for the bulk liquid material.

Recommendation: No additional acute studies are recommended. Although the available studies do not meet the requirements of the current OECD guidelines in most cases the available data fill the HPV required endpoints for acute toxicity. Conduct of additional acute toxicity studies would not add significantly to our understanding of this material's toxicity.

Repeat Dose Toxicity

There are several studies of Propargyl alcohol extending for 14 or 90-day periods by the three major routes of exposure. For the purposed of hazard and risk assessment the 90-day studies were reviewed relative to the HPV requirements. The table below summarizes the most important study by each route.

Route	Species	Sex	Organs Affected	Local NOAEL	Systemic NOAEL	Ref
Gavage	Rat	M	Liver, kidney		5 mg/kg	IRIS (33)
		F	Liver, kidney		5 mg/kg	
Inhal	Rat	M	Liver, kidney	16 ppm*	16 ppm	NTP (34)
		F	Liver, kidney	16 ppm*	16 ppm	
	Mouse	M	Liver, kidney	8 ppm	4 ppm	
		F	Liver, kidney	32 ppm	16 ppm	
Dermal	Rat	M	None		13.3 mg/kg	GAF (35)
		F	None		13.3 mg/kg	

* Excluding hyperplasia of the nose

Table 3: Repeated-dose Toxicity Studies of Propargyl Alcohol

Oral Exposure

The U.S.EPA sponsored an oral-gavage study in Sprague-Dawley rats of each sex using dose levels of 0, 5, 15 or 50 mg/kg (33). Administration of 15 or 50 mg/kg-day of Propargyl alcohol to rats for 13-weeks was associated with significant adverse effects on the liver and kidneys at 50 mg/kg and potentially adverse effects seen by histopathology at 15 mg/kg-day. The 50 mg/kg-day dose in males was also associated with reduced body weight gain, 20% mortality and reduction in hemoglobin, mean corpuscular volume and corpuscular hemoglobin. The low-dose, 5 mg/kg-day, was a NOAEL for rats of each sex. It should be noted that males appeared to be the more sensitive sex under these conditions as opposed to females, which were more sensitive in the acute studies.

Inhalation Exposure

The National Toxicology Program has completed 14-day and 13-week inhalation studies of Propargyl alcohol in Fischer 344 rats and B6C3F1 mice of each sex (34). In the rat studies, the most sensitive endpoint was

hyperplasia associated with the respiratory epithelium of the nose. Necrosis and atrophy of the respiratory epithelium was also observed along with weight changes in the liver and kidneys. Excluding the nasal hyperplasia and a decrease in cholinesterase, the NOAEL was 16 ppm for males and females.

In the mouse studies the livers and kidneys were also affected along with the respiratory epithelium. In addition, the two high-dose level (32 and 64 ppm) groups of mice had reduced red blood cells and hemoglobin. The NOAEL for male mice was 4 ppm and the NOAEL for female mice was 16 ppm.

Dermal Exposure

A study using dermal exposure of rabbits was conducted using a dosing regime of four administrations per day. That is the daily dose was dived into four equal portions and painted on the skin at four daily intervals. The dose levels (daily) were 1, 3 or 13.3 mg/kg and, other than minor skin irritation at the site of application, no adverse effects were observed that were associated with treatment (35).

Recommendation: No additional repeated-dose studies are recommended. The available data, much of which is modern and was conducted under GLP, fill the HPV required endpoint for repeated-dose toxicity.

Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate tests have been conducted that cover both of these endpoints.

Genetic Toxicology in vitro

Two *Salmonella typhimurium* reverse mutation assays, run with the standard strains and typical protocol, show lack of mutagenic activity in the presence or absence of metabolic activation (36, 37). There is, however, a report in the literature that in an unusual strain of *S. typhimurium* (strain D3052), in the absence of metabolic activation, Propargyl alcohol was a weak mutagen (15 revertants/mmol). As this is a strain with an intact excision repair, but without plasmid pKM101 that codes for the errorprone repair enzyme of the SOS system. The observed weak mutagenicity did not increase in the presence of a metabolic activation system (38). The results do not fit in with the standard strains used in the typical assays. There is also a notation in the NTP Chemical Status Report for Propargyl alcohol that it is positive in Salmonella (39). The NTP Salmonella data show that strain TA100 gave a weak positive response in the absence of metabolic activation when water was used as the solvent but not when DMSO was used as the solvent for the test substance. Also there was no positive response in the presence of metabolic activation using either induced rat or hamster liver S9. The overall call for mutagenicity of Propargyl alcohol was “negative” (40). At the request of the NTP, the data are not presented in a robust summary and only the results are included.

In a chromosome aberration test using CHO cells, cells collected 16 h following treatment with Propargyl alcohol showed a small but statistically significant increase in chromosomal aberrations in the absence of metabolic activation. Although only the response at the highest dose was significantly higher than the control, there was a positive trend. In the presence of metabolic activation, a larger, dose-related increase was induced. This effect was confirmed in two repeat experiments. In cells sampled 10 h following treatment, there was no increase in chromosomal aberrations, either with or without metabolic activation (41).

Genetic Toxicology in vivo

Mammalian genotoxicity was assessed *in vivo* using the mouse micronucleus test by at least two investigators. In an OECD-Guideline-474 study, a single gavage dose of Propargyl alcohol did not result in an increase in polychromatic erythrocytes containing micronuclei. It was concluded that the test material did not show genotoxic activity in this system (42). Another study in mice using two daily gavage doses of 0, 24, 48 or 72 mg/kg also gave negative results (41). In addition the NTP Chemical Status Report for Propargyl Alcohol also lists this material as negative in the micronucleus test (39). The NTP micronucleus data are from groups of 10 male and female mice exposed to either 0 or 64 ppm Propargyl alcohol for polychromatic erythrocytes; or exposed to 0, 4, 8, 16, 32 or 64 ppm Propargyl alcohol for norrmochromatic erythrocytes, by inhalation for 90 days. There was no increase in the number or percent of micronucleated cells (43)

Summary and Evaluation: Although there are some weak positive results in the "in vitro" testing, the iv vivo data from three micronucleus studies done under different dosing regimes indicate that these in vitro effects are not important in vivo.

Recommendation: The SIDS requirement for genetic testing has been met as assays sensitive to both point mutation and to clastogenic effects have been conducted using acceptable protocols. No additional testing is recommended.

Reproductive Toxicity

Examination of the reproductive organs after subchronic exposure to systemically toxic levels of Propargyl alcohol did not reveal any specific adverse effects on the reproductive organs of male or female animals. Data relative to the early events in developmental toxicology were not found.

Recommendation: It is recommended that additional data be generated that would be informative of the early events of development.

Developmental Toxicity

Some of the available data are potentially informative concerning the possibility of developmental toxicity by Propargyl alcohol. Specific developmental toxicity relies on the ability of Propargyl alcohol (or a metabolite of Propargyl alcohol) to gain access to the conceptus and then either a special sensitivity of developing tissue or the ability of the conceptus to bioactivate the molecule. Relative contributions of detoxifying systems in the conceptus are also a consideration. None of the available information precludes Propargyl alcohol from having the potential to gain access to the conceptus and to be bioactivated. The pharmacokinetics data indicate wide distribution of material (4), although the conceptus has not been specifically evaluated, it cannot be excluded. The putative activating enzyme CYP2E1 is expressed in the human fetus by 18 weeks of gestation (44). It has been proposed that fetal CYP2E1 has a different spectrum of activity and perhaps a different amino-acid sequence than adult enzyme, and this is actively under investigation (44). Sulik and coworkers are investigating the role of CYP2E1 in early embryos relative to the activation of ethanol (45). They are using knockout mice and have described planned research evaluating the role of free radical species and free radical protective systems in the conceptus.

The current mechanistic work will be informative but these results are unlikely to provide information that would definitively indicate that Propargyl alcohol is not a potential developmental toxin.

Recommendation: It is recommended that a developmental toxicity screening study be performed to obtain reliable information concerning the potential of Propargyl alcohol to induce specific developmental toxicity.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, the available information fills all of the requirements for physicochemical parameters, fate, acute and repeated-dose toxicity and genotoxicity. Regarding aquatic toxicity, it was determined that the fish and daphnia information was adequate while the algae data did not meet the HPV standards. It is recommended, however, that both daphnid (OECD 202) and algae (OECD 201) studies be conducted to improve the information available for this class of compounds. Other than data indicating lack of specific effects of Propargyl alcohol on reproductive organs, no reliable information on reproductive and developmental toxicity was found. For this reason, it is recommended that an OECD 421 "Reproductive/Developmental Toxicity Screening Test" be conducted on Propargyl alcohol. Based on the ADME results showing effective absorption and distribution by both oral and inhalation routes, either route could be effectively utilized.

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